REMARKS

1. STATUS OF CLAIMS

Claims 60, 61, 64-68, and 70-72 were pending in the application.

Claims 64-66 and 70 are canceled, without prejudice.

Claim 60 is amended to recite "**an anionic** matrix metalloproteinase inhibitor (MMPI)" to clarify that there is an ionic interaction between the MMPI and the polyionic polymer that allows for the extended release of the MMPI onto and into area contacted by the substrate. Support for the amendment is found in the specification as filed at paragraph [0049][1]. See also the recitation of **anionic** in claim 61. Claim 60 is also amended to recite "the C-terminal **carboxylic acid** form of ilomastat". See claim 65 for support. Claim 60 is amended to recite just the MMPIs recited in claim 65. Accordingly claims 64 and 65 are canceled.

Claim 60 is further amended to recite "wherein the polyionic polymer is a polymer of one or more allyl or vinyl monomers containing quaternary ammonium groups" to further specify the polyionic polymers applicable to the method. Support for this amendment is found at paragraph [0100] and claims 11 and 14 of the specification as filed.

Claim 61 is amended to recite "wherein the polyionic polymer is a polymer of one or more allyl or vinyl monomers containing quaternary ammonium groups" to narrow the scope of polyionic polymers applicable to the method. Support for this amendment is found at paragraph [0100] of the specification and claims 11 and 14 as filed.

Claims 60, 61, 67, 68, 71, and 72 are now pending in the application

2. THE OFFICE ACTION OF MARCH 4, 2009

Rejections

The Examiner, in a Non-Final Office Action mailed March 4, 2009, rejected all of the pending claims in the application.

A. Claim 61 was rejected under 35 U.S.C. § 102(b) as being anticipated by Ward et al. U.S. 5,575,993 ("Ward").

B. Claims 61 and 70-72 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Batich et al. U.S. Appl. 2002/0177828 ("Batich") in view of Ward.

C. Claims 60 and 64-68 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Batich in view of Schoenfeldt et al. U.S. Appl. 2002/0172708

[1] Citations herein to published patent applications are to the numbered paragraphs of the printed version.

("Schoenfeldt") and further in view of Voorhees et al. U.S. 2004/0235950 ("Voorhees").

3. THE INTERVIEW OF MAY 27, 2009

Applicants' counsel appreciatively acknowledge the Examiner's courtesy in conducting an interview by phone on May 27, 2009. The Examiner's description of the interview in the Examiner Interview Summary Sheet is accurate and complete and is incorporated by reference as Applicants' summary of the interview.

4. ARGUMENTS AGAINST EXAMINER'S REJECTIONS

Applicants respectfully traverse the Examiner's rejections of claims 60, 61, , 67, 68, 71, and 72 and request reconsideration and withdrawal of the rejections based on the above amendments and the following remarks.

A. REJECTION OF CLAIM 61 UNDER 35 U.S.C. § 102(b) AS BEING ANTICIPATED BY WARD.

The Examiner was not persuaded by Applicants' arguments filed December 12, 2008 regarding the distinction between Applicants' polyionic polymer being non-leachably bound to the substrate and the polymers of Ward which are not non-leachably bound. The Examiner explained that "just because the polymers [of Ward] may be washed off after their used [sic] as a wound bandage does not differentiate applicants claimed invention from that of Ward." Applicants respectfully disagree.

Applicants have amended claim 61 to limit the polyionic polymers recited in the claim to polymers of one or more allyl or vinyl monomers containing quaternary ammonium groups. The amendment further distinguishes the quaternary ammonium polymers recited in the claim of Applicants from the ionene polymers of Ward.

Applicants' invention embraces methods of treating skin ulcers, bed sores, and wounds with a substrate comprising a polyionic polymer comprising inherently antimicrobial quaternary ammonium polymer or copolymer **non-leachably** bound to the substrate. Typically the substrates of the invention are exposed to **aqueous bodily fluids** including blood, urine, menses, and sweat. Applicants assert that the normal use of a substrate involves contact with **aqueous bodily fluids**, for example blood and sweat. It is conceivable that the substrates of the invention would also be exposed to aqueous wash solutions during cleaning procedures such as hand or body washing. Applicants teach that the polymers of the invention are non-leachably bound to the substrate so that the polymers do not leach into these aqueous environments. Applicants' disclosure [0053, 0054, 0059, 0066, 0067][2], teaches that the polymers be non-leachably bound so that aqueous bodily fluids (blood, urine, menses, sweat, etc) do not leach the polymers from the substrate into the skin ulcers, bed sores, or wounds with which the substrate is in contact. It is

[2] Citations herein to published patent applications are to the numbered paragraphs of the printed version.

undesirable for the polymers of the invention to leach into the skin ulcers, bed sores, wounds, or similar environments. Furthermore, when the quaternary ammonium polymers are non-leachably bound to the substrate, the bonding prevents the depletion of the antimicrobial at its intended site, within the substrate.

Ward does not disclose a composition wherein the antimicrobial polymer is non-leachably bound to the substrate and does not leach into aqueous bodily fluids. Applicants have referred to Ward's disclosure [col 15, ln 2-4] that "the ionene polymer iodophors .... can be washed out using normal washing procedures" as an exemplification that the polymers are NOT non-leachably bound to the substrate. If they were **non-leachably** bound, then they would not leach from the substrate on exposure to the aqueous wash environment.

The Examiner asserted that the non-leachable characteristic of the polymer is an inherent aspects of the ionene polymers of Ward "because they have the same structure" and therefore the property is not distinguishable. Applicants disagree. Furthermore, Applicants claims now recite that they are polymers of one or more allyl or vinyl monomers containing quaternary ammonium groups, which is clearly different from those taught by Ward.

Claim 61 is a method claim which states that the recited inherently antimicrobial polymers are **non-leachably bound** to the substrate. Therefore the polymer is bonded to the substrate in such a way that it does not leach into the aqueous environments of bodily fluids such as blood, urine, menses, or sweat. Applicants define **non-leaching** to mean that "sections of the polymer of the present invention do not appreciably separate from the material ...under standard uses" [0066]. Furthermore, no less than 0.1 percent of the material separates [0066]. **Non-leachable** refers to the bond between the polymer chain and the substrate [0067].

Applicants' method of treating a wound requires that the polyquat polymer be **non-leachably** bound to the substrate. Ward teaches that the ionene polymers have an affinity for surfaces and can "adhere" to those surfaces [col 15, ln 12-18]. However, Ward also teaches that the polymers can be leached from the substrate. Ward exemplifies this teaching by the disclosure that the polymers are readily washed out using normal washing procedures [col 15, ln 2-4]. Therefore, Ward does not teach a method wherein the polyionic polymer is **non-leachably** bound to a substrate as recited by Applicants.

In order to anticipate a claim, the prior art reference must teach every element of the claim [MPEP § 2131]. Ward does not disclose the extended release characteristics and the non-leachability aspects of the polymer as recited in Applicants' claim 61. Because Ward does not disclose, expressly or inherently, all of the elements of claim 61, as currently amended, Ward cannot anticipate the claim. Applicants respectfully request the Examiner to withdraw the anticipation rejection of claim 61 and allow the claim.

B. REJECTION OF CLAIMS 61 and 70-72 UNDER 35 U.S.C. § 103(a) AS BEING UNPATENTABLE OVER BATICH IN VIEW OF WARD.

Applicants respectfully traverse the rejection and assert that Batich, in view of Ward, does not make claims 61, 71 and 72 obvious to one of ordinary skill in the art. The rejection is moot with respect to claim 70 because it is now canceled. Applicants reassert the arguments presented in their June 3, 2008 and December 12, 2008 responses.

The Examiner presents Batich as a primary reference for its disclosure of quaternary ammonium polymers. The Examiner admits that Batich does not disclose ionic association of an anionic antibiotic, analgesic, and/or anti-inflammatory with a quaternary ammonium polymer. The Examiner presents Ward as a secondary reference to combine with Batich to show that it was already known in the art that anionic antimicrobial compounds could be associated to cationic polymers. The Examiner further asserts that it would have been obvious to one of ordinary skill in the art that Batich and Ward are combinable. The Examiner concludes that it would be obvious to combine Batich and Ward to obtain Applicants' claimed method of treating a wound which comprises applying a material comprising a substrate which is non-leachably bound to a polyionic polymer which is ionically associated with an anionic antibiotic, analgesic, anti-inflammatory, or a combination thereof.

Claim 61 of the present application recites, among other limitations, that the "polyionic polymer is inherently antimicrobial and is non-leachably bound to said substrate." The claim further recites that "an antibiotic, analgesic, anti-inflammatory, or a combination thereof, [is] ionically associated with said polyionic polymer to achieve **extended release** of said antibiotic, analgesic, anti-inflammatory, or combination thereof onto and into said wound..." Even though Ward may teach that anionic antimicrobial compounds can be associated to cationic polymers, Ward provides no teaching or suggestion that anionic antimicrobial compounds can be associated with quaternary ammonium polymers to achieve **extended release** of the anionic antimicrobial compounds from the polymer. Batich also provides no teaching or suggestion that anionic antimicrobial compounds can be associated with quaternary ammonium polymers to achieve **extended release** of the anionic antimicrobial compouns from the polymer.

Applicants assert that Batich and Ward are not analogous art from the perspective of polymers being leachably or non-leachably bound to a substrate. One of ordinary skill in the art would not be motivated to combine these references. There is no reason for one of ordinary skill in the art to combine a reference disclosing non-leachable polymers with another reference disclosing leachable substances if the desired result is to obtain a non-leachablesubstance. As discussed above in section A, Ward does not teach or suggest that the cationic polymer be non-leachably bound to a substrate. Ward teaches that incorporation of certain bio-active compounds into an ionene polymer increases the solubility of the active material versus the bioactive alone. Thus, the resulting polymer is more prone to be soluble in water and dissolved [col 12, ln 21-34]. Ward also teaches that

iodinated ionene polymers impregnated in gauze and textiles are wound cleansing and disinfecting agents. However, those ionene polymers are readily washed (or leached) from the substrate [col 14, ln 61 to col 15, ln 4]. Ward does not teach or suggest that antimicrobial compounds be non-leachably bound to the substrate. Ward effectively teaches away from the concept of having a cationic antimicrobial polymer/anionic active agent wherein the cationic polymer is non-leachably bound to a substrate.

Applicants further assert that one of ordinary skill in the art would not have had a reason to combine method of using the non-leachably bonded antimicrobial polymers of Batich with use of readily soluble ionene polymers of Ward because, on their face, these are opposite concepts.

Batich discloses cationic polymers that are **non-leachably bound** to substrates. One of ordinary skill in the art would not consider the polymers of Ward which also have enhanced water solubility, as a source of ideas for improving the substances of Batich which would also retain their non-leaching characteristics. As explained above, Ward teaches away from that concept. Rather, Ward teaches the concept of a polymer being **leached** (washed) from a substrate.

Applicants therefore do not agree that it would be obvious to one skilled in the art to combine Batich with Ward. Furthermore, Under KSR it is legally insufficient to conclude that a claim is obvious just because each feature of a claim can be independently shown in the cited art. (*KSR International Co., v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727, 1741).

Furthermore, the Examiner has failed to show that the combination of Batich and Ward discloses all the features of Applicants' invention. Even though Batich may show quaternary ammonium polymers similar to Applicants' and Ward may show that biologically active anionic species can be "associated" with an ionene polymer, the combination does not suggest that one could produce a biologically active anionic species associated with a quaternary ammonium polymer which also has the features of non-leachably bonding the polymer to a surface and allowing extended release of the biologically active anionic material.

Applicants assert that the combination of Batich with Ward does not make obvious to one of ordinary skill in the art the invention as claimed in claims 61,71, and 72 of the instant application. Batich does not suggest combining anionic therapeutic agents with quaternary ammonium polymers to achieve extended release characteristics. Neither does Ward supply what is missing from the disclosure of Batich as discussed above with regard to claim 61.

Applicants respectfully request the Examiner to withdraw the obviousness rejection of claims 61, 70, and 72 and allow the claims as currently amended.

C. REJECTION OF CLAIMS 60 and 64-68 UNDER 35 U.S.C. § 103(a) AS BEING UNPATENTABLE OVER BATICH IN VIEW OF SCHOENFELDT AND VOORHEES.

Applicants respectfully traverse the rejection and submit that Batich, in view of Schoenfeldt and Voorhees, does not make amended claim 60 and claims, 67 and 68 obvious to one of ordinary skill in the art. The rejection is moot with respect to claims 64-66 because they are now canceled. Applicants have also amended claim 60 to recite that an **anionic** MMPI is associated with the quaternary ammonium polymer. Applicants have also narrowed the scope of recited MMPIs to include only GM1489 and the carboxylic acid salt form of illomastat, both of which are anionic at physiological pH. Applicants have also amended claim 60 to recite polymers of one or more allyl or vinyl monomers containing quaternary ammonium groups.

In the March 4, 2009 Office Action, the Examiner acknowledges that Batich does not disclose the use on skin ulcers, bed sores, or chronic wounds of the matrix metalloproteinase (MMP) inhibitors, ilomastat or GM1489. The Examiner further acknowledges that Batich fails to disclose or suggest ionic association of the actives (here MMPIs) with the inherently antimicrobial ammonium polymer taught in Batich. Applicants note that none of the references disclose a method wherein extended release of the MMPI is achieved when the anionic MMPI is ionically associated with the quaternary ammonium polymers recited in the present claims.

The Examiners cites Batich for its disclosure of quaternary ammonium polymers. The Examiner says that Schoenfeldt was used as secondary reference to show that it was already known in the art that ilomastat could be associated to cationic polymers. Voorhees was used for its disclosures of ilomastat and GM1489 as MMPIs. The Examiner concludes that it would be obvious to combine Batich, Schoenfeldt, and Voorhees to obtain Applicants' claimed method of treating skin ulcers, bed sores, or chronic wounds with a material comprising a substrate and a non-leachably bound quaternary ammonium polymer or copolymer wherein said polymer or copolymer is ionically associated with and achieves extended release of an MMPI such as ilomastat, GM1489, or C-terminal carboxylic acid form of ilomastat.

Applicants incorporate by reference and reassert their arguments concerning Batich, Schoenfeldt, and Voorhees presented in the June 3, 2008 and December 12, 2008 Responses and the Remarks concerning Batich above in Section B.

The Examiner was not persuaded by Applicants' arguments asserting that Schoenfeldt teaches away from using quaternary ammonium groups in the polymer backbone. Applicants further explain that a quaternary ammonium group must have **four non-hydrogen** substituents, for example four alkyl, aryl, or cycloakyl groups, attached to the nitrogen atom. Schoenfeldt does not disclose **quaternary** ammonium polymers as cationic groups. In paragraph [0041], Schoenfeldt discloses that the cationic groups linked to the polymer may be primary, secondary, or tertiary amines. In paragraph [0042], Schoenfeldt discloses that primary amines,

presumably protonated with acids to form **primary** ammonium salts, **are preferred**. One would infer from reading Schoenfeldt that it would be less desirable to replace the hydrogens of the primary amine with alkyl, aryl, or cycloalkyl groups. Thus, there is no reason for one of ordinary skill in the art to prepare for use with MMPIs polymers even of **secondary** or **tertiary** ammonium salts based on the teaching Schoenfeldt because these ammonium salts are less desirable. Schoenfeldt teaches that the amine is protonated with an acid to form the primary, secondary, or tertiary ammonium salt. Since the primary amines are **preferred**, a person having ordinary skill in the art who reads Schoenfeldt would conclude that tertiary amines (or ammonium), wherein the hydrogens of the primary amine is replaced by alkyl, aryl, or cycloalkyl groups, are **less preferred**.

But regardless of the foregoing, neither Batich nor Schoenfeldt provide any teaching of polymeric **quaternary** ammonium salts ionically associated with an anionic MMPI. Even if one wanted to incorporate the teachings of Schoenfeldt in Batich, no teaching is provided by either reference to demonstrate that it would be appropriate to ionically associate anionic MMPIs with a quaternary ammonium polymer for the medical uses recited in the present claim.

Schoenfeldt teaches that the anionic **polymers** protonate the amine-containing polymer to form the ammonium salt which have increased solubility [0025 – 0030]. Therefore, only primary, secondary, and tertiary ammonium compounds may be produced by such a process. The process described by Schoenfeldt is utterly unsuitable for introducing a fourth alkyl, aryl, or cycloalkyl substituent onto a tertiary amine to form a quaternary ammonium species as a monomer for forming such a polymer. One cannot prepare a quaternary ammonium salt by protonating a primary amine, or a secondary amine, or even a tertiary amine.

Schoenfeldt discloses that active ingredients (for example Illostat [sic]) are additives to the anionic-cationic polymer mixture added prior to freezing the solutions to form the sol gel [0051, 0055]. Schoenfeldt does not disclose that the active ingredients are ionically associated with the polymers. Thus, even if one of ordinary skill in the art were to look to Schoenfeldt to combine with the teachings of Batich, the worker would not be taught to prepare a quaternary ammonium salt having an ionically associated anionic MMPI because (1) adding a fourth alkyl, aryl, or cycloalkyl group to an amine would, according to Schoenfeldt, be even further removed from the desirable primary amine or primary ammonium, (2) Schoenfeldt fails to suggest a method for preparing monomers of quaternary ammonium moieties nor for preparing any such polymers incorporating an anionic MMPI therefrom, and (3) Batich does not disclose a method for ionically associating an anionic MMPI with a quaternary ammonium polymer to achieve extended release.

Schoenfeldt does not provide any disclosure or suggestion of quaternary ammonium polymers incorporating an ilomastat derivative. Even though Schoenfeldt may be interpreted to disclose primary, secondary, and tertiary ammonium polymers ionically bound to ilomastat, Schoenfeldt provides no teaching or suggestion to ionically bind a carboxylic acid derivative of ilomastat to

quaternary ammonium polymers.

Also, what Schoenfeldt discloses are non-fibrous porous materials – sol gels – which are aqueous dispersions of hydrated crosslinked particles [0061]. The sol gel comprises *inter alia* a hydrophilic polymeric component and one or more pharmaceutical medicaments [0018]. Schoenfeldt further explains that the hydrophilic polymeric component comprises polyionic/polyfunctional materials having opposite charges, for example one cationic polymer and one anionic polymer [0025, 0026, and 0027]. Schoenfeldt also discloses that the sol gels may constitute a part of a product (e.g. diaper) or be the product itself [0060]. Schoenfeldt does not teach that the pharmaceutical medicament (e.g. MMPI) be ionically associated with the polymeric component to "to achieve extended release of said matrix metalloproteinase inhibitor onto and into said skin ulcer, bed sore or chronic wound to reduce or eliminate endogenous matrix metalloproteinase activity in said skin ulcer, bed sore or chronic wound" as recited in Applicants' claim 60. Schoenfeldt also does not disclose that the hydrophilic polymers be inherently antimicrobial nor are they non-leachably bound to a substrate.

In contrast, in Applicants' claimed method, inherently antimicrobial polymers are chemically attached (bonded) to a substrate (e.g. wound dressing). Applicants' invention as recited in amended claim 60 and claims 64-68 is to methods of treating skin ulcers, bed sores, or chronic wounds with a material comprising a substrate, an antimicrobial polymers non-leachably bound to said substrate which imparts antimicrobial properties to the substrate, and an anionic MMPI which is ionically associated with the polymer to achieve extended release of said anionic antibiotic, analgesic, anti-inflammatory, or a combination thereof. Applicants have amended claim 60 to recite expressly that the MMPI is anionic. The claim recites that it is ionically associated with the antimicrobial polymer. Sol gel is a different art – and would not be considered as a basis for one of ordinary skill in the art to prepare polymers non-leachably bound to substrates.

Batich also discloses antimicrobial polymers that are non-leachably bound to a substrate. However, Applicants' invention further comprises the use of anionic MMPIs that are released from the substrate to achieve extended retention and release characteristics [see 0063].

Applicants agree with the Examiner's statement that the each individual secondary reference applied under 35 U.S.C. § 103 does not have to disclose **all** of the elements recited in Applicants' claim. However, the reference must teach the element that is to be combined with another reference lacking that element so that when combined, all of the elements recited in Applicants' claim are shown in the combined prior art references. The Examiner admits that Batich does not disclose anionic MMPIs ionically associated with a quaternary ammonium polymer. Applicant points out that Schoenfeldt does not disclose a method of ionically associating an anionic MMPI with a quaternary ammonium polymer. Voorhees also does not disclose or suggest the use of polymeric quaternary ammonium moieties. Not one, not any two, nor all three of these references taken together disclose a method of treating skin ulcers, bed sores, or chronic wounds with a material

comprising a quaternary ammonium polymer ionically associated with an MMPI to achieve extended release as recited in claim 60. That combination of element is missing from the cited references.

Moreover, the method of treatment using materials having extended release of anionic actives is not disclosed or taught in Batich, or in Schoenfeldt, or in Voorhees. Therefore, Applicants assert that it is not possible for one of ordinary skill in the art to have found any reason from the cited references to develop Applicants' claimed invention with respect to extended release of the MMPI bioactive materials.

Therefore, Applicants respectfully submit that the combination of Batich, Schoenfeldt, and Voorhees does not make obvious the invention as claimed. Applicants respectfully request the Examiner to withdraw the obviousness rejection of claims 60, 67, and 68 and allow the claims as currently amended.

CONCLUSION

Applicants respectfully traverse all of the rejections. Claim 61 is not anticipated because the prior art does not disclose each and every element of the claim. Claims 60 and 67-68 are not made obvious to one of ordinary skill in the art by the disclosures of Batich, Schoenfeldt, and Voorhees as described above. Claims 61 and 70-72 are not made obvious to one of ordinary skill in the art by the disclosures of Batich, and Ward as described above.

For the foregoing reasons, Applicants submit that the claims presented herewith are patentable over the prior art of record and respectfully solicits prompt action thereon. If any questions remain, the Examiner is invited to phone the undersigned attorneys.

Respectfully submitted: June 4, 2009

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